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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,643	12/12/2001	Thomas C. Terwilliger	S-96,583	7287
35068	7590	05/09/2005	EXAMINER	
UNIVERSITY OF CALIFORNIA LOS ALAMOS NATIONAL LABORATORY P.O. BOX 1663, MS A187 LOS ALAMOS, NM 87545			DEJONG, ERIC S	
			ART UNIT	PAPER NUMBER
			1631	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	10/017,643		TERWILLIGER, THOMAS C.	
	<b>Examiner</b>		<b>Art Unit</b>	
	Eric S. DeJong		1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 28 January 2005.
- 2a) ☒ This action is FINAL.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                         |                                                                             |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____                                                |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____                                                             | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

Applicants' arguments, filed 28 January 2005, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The amendment filed by applicants on 28 January 2005 containing amendments to the specification, an amended set of claims, and a response to the previous office action is acknowledged. Claims 1-8 are currently under examination.

### ***Specification***

The disclosure is objected to because of the following informalities:

It is noted that the amendment, filed on 28 January 2005, states "U.S. patent application S.N. 09/769,612, filed January 23, 2004, now U.S. Patent 6,721,661, issued April 13, 2004" is incorrect as said application issued as U.S. Patent 6,721,664. Further, the citation in said amendment to the specification that U.S. application 09/512,962 is "now allowed" is improper. The status of an application should be amended only when the prior application is either issued as a U.S. patent or abandoned.

The specification on page 14 recites "Figures 1A-1B" and again on page 15, recites "Figure 1A". The actual drawings filed on 12/12/01 only contain Figure 1, no Figure 1A or 1B. The same is true for the recitation of Figures 7A and 7B on page 18.

Appropriate corrections are required.

***Vagueness and Indefiniteness***

Applicants arguments and amendments to the claims are found convincing regarding the previous rejection under 35 U.S.C. 112, second paragraph is hereby withdrawn.

***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Murshudov et al. This rejection is newly applied and necessitated by amendment to the instant claims.

Claim 1: Murshudov et al. discloses the application of maximum likelihood calculations to improve x-ray structural refinement and determination methodologies and reduce model bias in map calculations (a method for improving an electron density map representing a crystal structure, minimum bias from known electron density maps). See Murshudov et al., page 241, column 2, lines 18-50 and page 242, column 1, lines 24-38. Murshudov et al. provides a basis for the computations of maximum likelihood with an evaluation of the posterior probability distribution,  $P$ , which incorporates the experimental data  $|F|$ , wherein  $|F|$  is defined as experimental amplitude of the structure factors obtained by x-ray crystallography (step (a) obtaining x-ray diffraction observed structure factor amplitudes for a plurality of reflections). See Murshudov et al., at least page 240, column 1, lines 25 and 26 and page 242, column 1, line 46 through column 2, line 8. In calculating the conditional probability distribution, a function that combines

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structure factor amplitude and phase information, Murshudov et al. acknowledges that experimental phases are usually not known and accommodates the separate component containing phase information for each reflection as a distribution of phases defined as  $P(\phi)$  (step (b) selecting a starting set of crystallographic phases to combine with the observed structure factor amplitudes). Further, solving the expression provided in equation 8 provides an evaluation of crystallographic structure factors and under a reasonably broad interpretation reads on the claimed first set of structure factors. See Murshudov et al., page 243, column 1, line 9 through page 244, column 2, line 12 and equations 8 and 9. Murshudov et al. further provides examples of using the above calculation in building partial models built on experimentally phased maps and using said maps to generate a useful contribution to the calculated structure factor (step (c) deriving a first electron density map from the first set of structure factors; step (d) identifying features of the first electron density map to obtain expected distributions of electron density; step (e) making a comparison between the first electron density map and the expected distributions of electron density). See Murshudov et al., page 243, column 2, lines 1-23, page 248, figure 2, and page 249, column 1, lines 1-15. In examples applications of the disclosed methodology, Murshudov et al. teach the evaluation of differences between calculated phases determined from current and final models at all stages of the refinement process, which reads on the claimed step (f) estimating how changes in the crystallographic phase of a reflection  $k$  affect the comparison. See Murshudov et al., page 246, column 1, line 15 through column 2, line 2. Murshudov et al. discloses derivative forms of the log-likelihood which rely on an

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evaluation of the prior distribution of phases,  $P(\phi)$ , and is utilized in evaluating the minimization of the maximum likelihood function that is utilized in the above described refinement procedures (step (g) establishing crystallographic phase probability distributions from the comparisons for the possible crystallographic phases of reflection  $k$ ). See Murshudov et al., page 251, column 2, line 1 through page 252, column 2, line 26. Further, the above described refinement methodology is recursively performed and evaluated on a number of crystallographic reflections and reads on the claimed method steps of repeating steps (c) through (g) as  $k$  is indexed through all of the plurality of reflections. See Murshudov et al., page 245, column 1, line 24 through column 2, line 35.

Murshudov et al. further provides examples where several successive rounds of the above refinement procedures was used to improve upon pre-existing modeling attempts and ultimately produced a final set of structure factors, wherein amplitudes and final phase estimates were combined, that are in turn used to produce electron density maps representing a given protein structure (step (j) deriving an updated electron density map; step (k) repeating steps (d) through (j); step (l) forming a final electron density map using the final set of crystallographic phases). See Murshudov et al. page 247, column 1, line 4 through page 248, column 2, line 8, and Tables 1-3, and Figure 2C.

Claim 2: Murshudov et al. teaches that in the structure refinement and modeling procedure, accommodating identified regions of structure and bulk solvent is handled by

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additions to the structure factor by modifying equation 9, the expression for probability distribution (making probability estimates of whether each point in the map is located in a solvent region or crystal structure region). See Murshudov et al., page 250, column 2, lines 1-41.

Claim 3: In defining the coordinates and form factors for each atom using the Miller index of the reflecting plane, Murshudov et al. teaches that the derivatives of the coordinates can be used in a form function that has the same symmetry as the Patterson function, which under a reasonably broad interpretation reads on the claimed identification of features of the electron density map includes estimates at each point in the map is related by non-crystallographic symmetry to electron density at another point in the map. See Murshudov et al., page 253, column 1, line 1 through column 2 line 17 and equations 42-49.

Claims 4 and 5: Murshudov et al. provides examples of the disclosed refinement method applied to the x-ray crystal structure of cytochrome c', which comprises 8 separate  $\alpha$ -helices. The refinement methodology included an initial electron density map determined by a different refinement method and allowed for comparison determinations between intermediate and final electron density map calculations (wherein identifying features of the electron density map includes estimates of whether a structural motif is located at each map point; wherein the structural motif is a helix). See Figure 2 and pages 247, column 1, line 21 through page 249, column 1, line 15.

Claim 6: The refinement methodology disclosed by Murshudov et al. relies upon log-likelihood functions to define and evaluate phase probability distributions (the crystallographic phase probability distributions are log-likelihood functions). See at least Murshudov et al., equations 8-14 and page 243, column 1, line 5 through page 244, column 2, line 12.

Claim 7: Murshudov et al. discloses first and second derivatives of log-likelihood functions pertaining to the determination of the distribution of phases as well as Fast-Fourier Transform operations in determining maximum likelihood through the minimization procedures of said likelihood functions (steps of calculating first and second derivatives; applying a Fast Fourier Transform based algorithm to determine probable crystallographic phase probability distributions). See Murshudov et al., page 253, column 1, line 13 through page 253, column 2, line 26 and equations 24-40.

Claim 8: The disclosed example of cytochrome c' modeling and refinement by Murshudov et al. reads on the claimed selecting a model crystal structure having similarities to the crystal structure being examined. Further, Murshudov et al. teaches that the current methodologies are improvements upon previous refinement strategies well known in the art that utilize wherein structure factor amplitudes are weighted in order to reduce refinement bias (assigning a low weighting factor to structure factors of the model crystal; combining the weighted structure factors with the observed structure



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factors for deriving the first electron density map). See Murshudov et al., page 241, column 1, line 24 through column 2, line 17.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone

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number for the organization where this application or proceeding is assigned is (571) 272-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

EDJ

*EDJ*

*Ardin H. Marschel 5/3/05*  
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PRIMARY EXAMINER